General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of *G6PD* deficiency genotype.

Bibliographic Source(s)

Relling MV, McDonagh EM, Chang T, Caudle KE, McLeod HL, Haidar CE, Klein T, Luzzatto L. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. Clin Pharmacol Ther. 2014 Aug;96(2):169-74. [38 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Genetic Test Interpretation

The *G6PD* gene is on the X chromosome (Xq28;ref.2). Genotype results associated with G6PD deficiency may be reported as (i) hemizygous male (e.g., one class I–III variant allele), (ii) homozygous female (two identical deficient class I–III alleles with the same variant), (iii) compound heterozygous female (two different deficient class I–III alleles with different variants), and (iv) heterozygous female (one normal class IV allele and one deficient class I–III allele) (Table 1, below). The known inactivating or low-function variants (class I, II, and III variants) are provided in Supplementary Table S1 online (see the "Availability of Companion Documents" field). If these variants are present, they may be interpreted as defined in Table 1, below, and in some cases a diagnosis of G6PD deficiency can be made on the basis of genotypic results. Hemizygous males, homozygous females, and compound heterozygous females are classified as either G6PD deficient or G6PD deficient with chronic nonspherocytic hemolytic anemia (CNSHA) (Table 1, below). For the rare male patients who have an extra X chromosome (i.e., Klinefelter's syndrome), *G6PD* genotype should be interpreted as if they are females.

Determining G6PD phenotype in heterozygous females (one normal class IV allele and one deficient class I–III allele) is not possible based on genetic testing alone due to X-linked chromosome inactivation in females. This X-chromosome inactivation, which can happen in a variable percentage of somatic cells, inactivates either the normal or the low-activity allele and translates into heterozygous females having a mosaic of G6PD-normal and G6PD-deficient erythrocytes. The resulting overall enzyme activity will be variable because the ratio of the two types of red cells is highly variable and can change over time in the same individual. Thus, G6PD activity in heterozygous females can potentially go the full

range from being normal to being G6PD deficient, and thus heterozygotes may display a drug-induced acute hemolytic anemia (AHA) profile similar to that of homozygotes (see the Supplementary Material online [*G6PD* Heterozygotes section] [see the "Availability of Companion Documents" field]). Thus, an enzyme activity test is needed to assign G6PD phenotype in heterozygous females.

Because most genetic tests do not comprehensively interrogate all variants associated with G6PD deficiency and because the phenotype of genotypically proven heterozygous females is unpredictable, most diagnoses of G6PD deficiency are currently made via tests of enzyme activity rather than genotype. In males, the results of G6PD enzyme activity are usually clear cut, including in newborns, who tend to have higher activity than that observed in older children and adults. The primary risk of misclassification in males is when there has been recent hemolysis (because G6PD in reticulocytes and in young erythrocytes is higher) or recent blood transfusion (because the transfused blood is likely to be G6PD normal); either or both may shift a G6PD-deficient enzyme level near to or even within the normal range. In females, there may be overlap in activity between G6PD homozygous normal and heterozygotes and between heterozygotes and homozygous deficient; there may be also more intrasubject variability in G6PD activity than in males (see the Supplementary Material online [*G6PD* Heterozygotes section] [see the "Availability of Companion Documents" field]). Universal neonatal screening programs for G6PD deficiency via the use of semiquantitative fluorescent spot test or quantitative enzyme activity assay have been instituted or proposed in areas with a high incidence of G6PD deficiency such as Asia, Europe, Africa, and the Middle East (see Supplementary Tables S3 and S4 online [see the "Availability of Companion Documents" field] for frequencies in major racial/ethnic groups).

Table 1. Assignment of Likely G6PD Phenotypes Based on Genotype/Diplotype

Likely Phenotype	Definition	Genotypes	WHO Class for *G6PD* Variants[a]	Example of Diplotypes[b]
Normal	Very mild or no enzyme deficiency (>60% of normal enzyme levels)	A male carrying a nondeficient (class IV) allele	IV	B, Sao Boria
		A female carrying two nondeficient (class IV) alleles	IV/IV	B/B, B/Sao Boria
Deficient	<10–60% of normal enzyme activity	A male carrying a deficient (class II–III) allele	II, III	A–, Orissa, Kalyan-Kerala, Mediterranean, Canton, Chatham
		A female carrying two deficient (class II–III variants) alleles	II/II, II/III, III/III	A–/A–, A–/Orissa, Orissa/Kalyan-Kerala, Mediterranean/Mediterranean, Chatham/Mediterranean, Canton/Viangchan
Deficient with CNHSA	Severe enzyme deficiency (<10% activity) and associated with CNHSA	A male carrying a class I allele	I	Bangkok, Villeurbanne
		A female carrying two deficient (class I variants) alleles	I/I	Bangkok/Bangkok, Bangkok/Villeurbanne
Variable[c]	Normal or deficient enzyme activity	A female carrying one nondeficient (class IV) and one deficient (class I–III variants) allele	IV/I, IV/II, IV/III	B/A–, B/Mediterranean, B/Bangkok

CNSHA, chronic nonspherocytic hemolytic anemia; WHO, World Health Organization.

[a]WHO classifications from reference 14, other details from reference 17 in the original guideline document. Class I variants are extremely rare; the distinction between class II and III variants is not clear, and the "class V" very high activity variant has been reported in only a single case. Therefore, almost all patients will carry class II, III, or IV alleles. It should be noted that the class of a variant may have been assigned only by the clinical manifestations of a patient in which the variant was subsequently identified.

[b]Due to the large number of *G6PD* variants, many other diplotypes may be possible besides those given as examples here; see Supplementary Table S1 online (see the "Availability of Companion Documents" field) for a more comprehensive list of variant alleles with their assigned WHO class.

[c]Due to X-linked mosaicism, females heterozygous for one nondeficient (class IV) and one deficient (class I–III variants) allele may display a normal or a deficient phenotype. It is therefore difficult to predict the phenotype of these individuals (Supplementary Material online [*G6PD* Heterozygotes section]).

Therapeutic Recommendations

Rasburicase use is contraindicated by the U.S. Food and Drug Administration (FDA), the European Medicines Agency, and the Pharmaceuticals and Medical Devices Agency in those with G6PD deficiency (see Table 2 and Figure 1 in the original guideline document). If, on the basis of genotyping, a deficient status can be unambiguously assigned to a patient, that would be a sufficient contraindication to the use of rasburicase. However, due to the limitations of genetic testing, in most cases it is necessary to perform G6PD enzyme testing to assign G6PD status at this time.

The FDA recommends that patients at higher risk of G6PD deficiency, such as those with African or Mediterranean ancestry, be tested for G6PD deficiency before initiation of rasburicase. However, it should be noted that patients of all ancestries may be G6PD deficient. The drug labels do not specifically mention genetic testing, but with the increased availability of genetic test results some patients may be diagnosed with G6PD deficiency preemptively; if so, such definitive results could be used to preclude prescribing of rasburicase and potentially other oxidative drugs even in the absence of G6PD enzyme activity results.

Pediatrics

Much of the evidence relating G6PD deficiency to rasburicase-induced hemolysis and methemoglobinemia was generated in neonates or children (see Supplementary Table S7 online [see the "Availability of Companion Documents" field]), and thus these guidelines apply to neonates, children, and adults.

Recommendations for Incidental Findings

Patients with G6PD deficiency should be advised that they are at an increased risk of hemolysis after exposure to fava beans or to high-risk drugs or chemicals (Supplementary Table S6 online), and that it is recommended to avoid such compounds (see the Supplementary Material online [Unsafe Drugs for G6PD Deficient Patients section] and Supplementary Table S6 online [see the "Availability of Companion Documents" field]).

Table 2. Recommended Therapeutic Use of Rasburicase in Relation to G6PD Phenotype

G6PD Phenotype	Implications for Phenotypic Measures	Dosing Recommendations for Rasburicase	Classification of Recommendations[a]
Normal[b]	Low or reduced risk of hemolytic anemia	No reason to withhold rasburicase based on G6PD status[b]	Strong
Deficient or deficient with CNSHA	At risk of acute hemolytic anemia	Rasburicase is contraindicated; alternatives include allopurinol[c]	Strong
Variable[b]	Unknown risk of hemolytic anemia	To ascertain that G6PD status is normal, enzyme activity must be measured; alternatives include allopurinol[c]	Moderate

CNSHA, chronic nonspherocytic hemolytic anemia.

[a]Rating scheme described in Supplementary Material online (see the "Rating Scheme for the Strength of the Recommendations" or "Availability of Companion Documents" fields).

[b]A negative or inconclusive genetic test cannot be assumed to indicate normal G6PD phenotype; an enzyme activity test is needed to assign G6PD phenotype in such cases.

[c]Allopurinol is associated with severe cutaneous reactions in the rare carriers of the *HLA-B*58:01* allele.

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

An algorithm titled "Workflow for Interpreting *G6PD* Genotype and for Assessing the Need for an Enzyme Activity Test" is provided in the original guideline document.

Scope

Disease/Condition(s)

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Tumor lysis syndrome

Guideline Category

Risk Assessment

Treatment

Clinical Specialty

Hematology

Internal Medicine

Medical Genetics

Nephrology

Oncology

Pediatrics

Pharmacology

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To help interpret the results of clinical *G6PD* genotype tests so that they can guide the use of rasburicase

Note: Detailed guidelines on other aspects of the use of rasburicase, including analyses of cost-effectiveness, are beyond the scope of this document.

Target Population

Neonates, children, and adults being considered for rasburicase therapy

Interventions and Practices Considered

Rasburicase therapy

Major Outcomes Considered

Adverse effects of rasburicase therapy in relation to *G6PD* genotype

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The authors searched the PubMed database (1966 to August 2013) and OVID MEDLINE (1950 to August 2013) for keywords (rasburicase OR urate oxidase OR uricase OR elitek OR Fasturtec) AND (G6PD OR glucose-6-phosphate dehydrogenase OR G-6-PD). General searches for (rasburicase OR urate oxidase OR uricase OR elitek OR Fasturtec) and (G6PD OR glucose-6-phosphate dehydrogenase OR G-6-PD) were also carried out. Definitive reviews were relied upon to summarize much of the earlier literature.

Using the specified search criteria, 14247 publications were identified (after excluding non-English manuscripts). Inclusion criteria included publications that included *in vivo* clinical outcome (i.e., acute hemolysis or methemoglobinemia) for rasburicase or urate oxidase in G6PD deficient individuals (as determined by enzyme assay), *in vivo* clinical outcome (i.e., acute hemolysis or methemoglobinemia) for rasburicase or urate oxidase in G6PD deficient individuals (as determined by genotype), *in vivo* clinical outcome (i.e., acute hemolysis or methemoglobinemia) for rasburicase or urate oxidase in normal G6PD individuals (as determined by genotype or enzyme assay) that developed acute hemolysis after exposure to rasburicase.

Number of Source Documents

Following application of the inclusion criteria, 18 publications were reviewed and included in the evidence table.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence Linking Genotype to Phenotype

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The evidence linking *G6PD* genotype to phenotype (adverse reaction to rasburicase) is summarized in Supplemental Table S7 online (see the "Availability of Companion Documents" field) and is graded using a scale modified slightly from Valdes et al. (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. The authors chose to use a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf) (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of rasburicase in the context of glucose-6-phosphate dehydrogenase (G6PD) deficiency genotype

Potential Harms

Administration of rasburicase to G6PD-deficient patients has resulted in cases of subsequent hemolytic anemia and methemoglobinemia, which can be fatal (see Supplementary Table S7 online [see the "Availability of Companion Documents" field]). Of course, tumor lysis syndrome can itself be life-threatening, and alternative uric acid–lowering therapy, such as allopurinol, may not be as efficacious as rasburicase at lowering uric acid levels and has other potential side effects. The risk of severe acute hemolytic anemia (AHA) and possible methemoglobinemia potentially caused by rasburicase versus the risk of tumor lysis syndrome complications if rasburicase is not used must be weighed against each other.

Contraindications

Contraindications

Rasburicase is contraindicated for use in patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency by the U.S. Food and Drug Administration (FDA), the European Medicines Agency, and Japan's Pharmaceuticals and Medical Devices Agency due to the risk of acute hemolytic anemia (AHA) and possibly methemoglobinemia (see the "Potential Harms" field).

Qualifying Statements

Qualifying Statements

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines or for any errors or omissions.

Other Considerations

Recommendations for the testing of other genetic markers are beyond the scope of this guideline. Agents known to induce or inhibit glucose-6-phosphate dehydrogenase (G6PD) expression may also influence the risk of rasburicase-induced hemolysis. Variation in the pharmacokinetics of

rasburicase and dosage prescribed could also affect risk.

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

Several commercially available genetic tests screen only for some of the more common G6PD genetic variants. Therefore, any patient could have a rare, different, or previously unknown genetic variant; thus, a genetic test may have been reported as "negative," but the patient could nonetheless have G6PD deficiency.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Relling MV, McDonagh EM, Chang T, Caudle KE, McLeod HL, Haidar CE, Klein T, Luzzatto L. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for rasburicase therapy in the context of G6PD deficiency genotype. Clin Pharmacol Ther. 2014 Aug;96(2):169-74. [38 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Aug

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

Source(s) of Funding

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Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The authors declared no conflict of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Pharmacogenomics Knowledgebase Web site .

Availability of Companion Documents

The following is available:

- Supplementary material, including tables and methodological information, is available from the Pharmacogenomics Knowledgebase Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 4, 2014. The information was verified by the guideline developer on January 23, 2015.

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